

REMARKS

Claims 1-9 and 11-22 are pending. Claims 23-30 have been withdrawn as being directed to a non-elected invention. Claims 2 and 11-22 are being cancelled herewith. Claims 1-9 are currently under examination in the present application. All of the claims under examination stand rejected. Claim 1 is being amended herewith. Support for this amendment can be found throughout the specification. Following entry of the present amendments, Claim 1-9 will be pending and subject to further examination. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

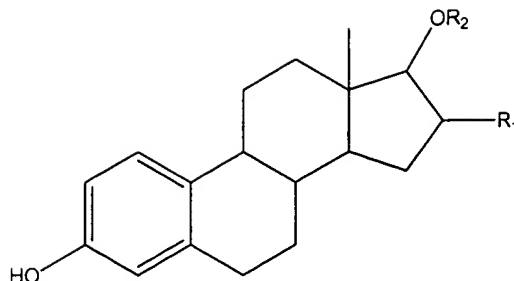
The Office Action

Claims 1, 3-5, 7, 8, 11, 13, 18 and 21 were rejected under 35 U.S.C. 102(b) as being anticipated by GB 1,570,597. Claims 11-22 were rejected under 35 U.S.C. 103(a) as being obvious and unpatentable over GB 1,570,597. Claims 1-9 and 11-22 were rejected under 35 U.S.C. 103(a) as being obvious and unpatentable over the patent to Ram et al. (U.S. Patent No. 6,136,992). Applicants respectfully traverse the foregoing rejections.

The Rejection Under 35 U.S.C. §102(a)

Claims 1, 3-5, 7, 8, 11, 13, 18 and 21 were rejected under 35 U.S.C. 102(b) as being anticipated by GB 1,570,597. The Examiner states that GB 1,570,597 discloses 16 β -ethylestradiol. Applicants admit that GB 1,570,597 discloses 16 β -ethylestradiol, but respectfully disagree that GB 1,570,597 anticipates Claims 1-9.

GB 1,570,597 discloses a compound having the following structure:



where R_1 is alkyl or alkenyl of 2 or more carbons and R_2 is hydrogen or acyl. R_1 can be ethyl thereby making 16 β -ethylestradiol.

However, comparing the disclosure of GB 1,570,597 to the present invention, GB 1,570,597 requires R_a to be H and only H. No other substituent is possible at the 2-position of the compound disclosed in GB 1,570,597. In contrast, the present invention requires R_a to be - N_3 , - $C\equiv C-R$, - $CH=CH-R$, - $R-CH=CH_2$, - $C\equiv CH$, - $R-R_1$, - $OC(O)CH_3$, - $C(O)H$, - NH_2 , - NMe_2 , or - $NHMe$, where R is a straight or branched alkyl with up to 10 carbons or aralkyl, and R_1 is -OH, - NH_2 , -Cl, -Br, -I, -F or CF_3 . In claims 1-9 of the present application, R_a can never be H.

In order for a reference to anticipate a claim, the reference must disclose each and every limitation of the claim. Since none of Claims 1-9 include the limitation that R_a is -H, GB 1,570,597 does not disclose each and every limitation of those claims. Therefore, GB 1,570,597 cannot anticipate Claims 1-9. Accordingly, applicants respectfully submit that the rejection of Claims 1-9 under 35 U.S.C. §102 is improper and should be withdrawn.

The Rejection Under 35 U.S.C. §103

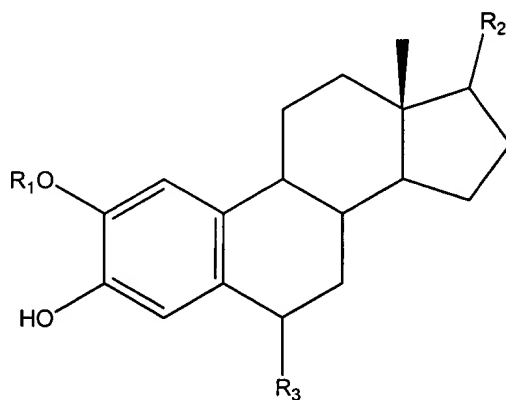
Claims 11-22 were rejected under 35 U.S.C. 103(a) as being obvious and unpatentable over GB 1,570,597. Applicants are canceling herewith Claims 11-22. Therefore, the rejection of Claims 11-22 under 35 U.S.C. 103(a) is moot.

Claims 1-9 and 11-22 were also rejected under 35 U.S.C. 103(a) as being obvious and unpatentable over the patent to Ram et al. The rejection point specifically to Formula (I) of

Ram et al. The rejection states that Ram et al. discloses estradiol derivatives encompassed by Claims 1-9 and 11-22. The rejection further states that the presently claimed invention differs from the reference in claiming one of the R_{h1} or R_{h2} as an alkyl group. The rejection further notes the proviso of Claim 1, but contends that the invention differs from the prior art by a single methyl group thereby making the claimed compound a homologue of the prior art. Applicants disagree.

Applicants agree that Ram et al. discloses alkyl estradiols. However, applicants disagree that the presently claimed compounds are homologs of the compound disclosed in Ram et al.

The Formula (I) referenced in the Office Action is merely 2-methoxyestradiol, a compound that is prior art to Ram et al. Ram et al. also discloses a genus of compounds he claims as his invention as follows:



wherein, R_1 is C1—C6 lower alkyl or substituted lower alky, R_2 is $-OH$ or $-NH_2$, and R_3 is selected from the group consisting of $=O$, $-H$, $=N-NH_2$, $=N-NH-SO_2$ -(lower alkyl), $=N-NH_2$, $=N-NH-SO_2$ -(substituted lower alkyl), $=N-NH-SO_2$ -phenyl, $=N-NH-SO_2$ -(substituted phenyl), $=N-OH$, $=N-O$ -(lower alkyl), and $=N-O$ -(substituted lower alkyl), provided that R_3 is not $-H$ or $=O$ if R_2 is methyl. From the foregoing, it is clear that the presently claimed invention differs from the genus disclosed in Ram et al. by more than a methyl group. Ram et al. requires R_3 to

not be -H (*i.e.*, substituted) when R₂ is -OH; whereas, in the claimed invention the 6-position must always be -H (*i.e.*, unsubstituted) and the 17-position must always be -OH. Ram et al. requires the 16-position to be unsubstituted; whereas, the presently claimed invention requires the 16-position to be at least singly substituted by those items listed in Claim 1 for R_{h1} or R_{h2}. Furthermore, Ram et al. requires the 2-position to be an alkoxy or a substituted alkoxy; whereas, the presently claimed invention does not include an alkoxy or a substituted alkoxy at the 2-position. Thus, the presently claimed invention differs from the alleged invention disclosed by Ram et al. in at least three different ways at three different locations on the molecule; *i.e.*, the 2-position, the 6-position and the 16-position.

A comparison of the presently claimed invention to 2-methoxyestradiol reveals similar distinctions. 2-methoxyestradiol requires a methoxy group at the 2-position; whereas, the presently claimed invention does not permit either a methoxy group or an alkoxy group at the 2-position. 2-methoxyestradiol requires the 16-position to be unsubstituted; whereas, the presently claimed invention requires the 16-position to be at least singly substituted by those items listed in Claim 1 for R_{h1} or R_{h2}. Thus, the presently claimed invention differs from 2-methoxyestradiol, 2-alkoxyestradiols or 2-substituted alkoxyestradiols in at least two different ways at two different locations on the molecule; *i.e.*, the 2-position and the 16-position.

It is respectfully submitted that a compound that differs from a prior art compound by at least two different groups at two different locations on a multi-membered steroid ring structure is not a homolog. There is no structural similarity between the compounds disclosed in Ram et al. and the presently claimed invention, other than sharing the same general steroidal ring backbone structure; *i.e.*, rings A, B C and D. This very low level of structural similarity does not suggest that the prior art compounds and the presently claimed compounds would have similar physical properties.

Furthermore, Section 2144.09 of the MPEP discusses the subject of structural similarity between chemicals. Although the present claims do not involve homologues, the MPEP makes it clear that even if compounds are homologous, homology should not be automatically equated with prima facie obviousness because the claimed invention and the prior art must each be viewed “as a whole.” MPEP §2144.09. Thus, it would be erroneous for the examiner to contend that the present claims are *prima facie* obvious merely because of alleged homology or structural similarity. The examiner must consider the claimed invention and the prior art as a whole in making a determination of alleged obviousness. Thus, the problem of deactivation discovered by applicants and the solution of that problem by substituting estradiols at both the 2- and the 16-position to provide bulk hindrance to deactivation mechanisms must also be considered.

To illustrate how the claimed invention and the prior art must be considered as a whole, the MPEP discusses the case of *In re Langer*, 465 F.2d 896 (CCPA 1972). The MPEP states, “Claims to a polymerization process using a sterically hindered amine were held unobvious over a similar prior art process because the prior art disclosed a large number of unhindered amines and only one sterically hindered amine (which differed from the claimed amine by 3 carbon atoms), and therefore the reference as a whole did not apprise the ordinary artisan of the significance of hindered amines as a class.)” MPEP §2144.09.

The same principal of law is applicable in the present case. In the present case the prior art does not disclose sterically hindering degradation of the hydroxyl group substituted at the 17-position by using bulk-hindering substituents substituted at the 16-position. In fact, Ram et al. disclose that its compounds must be unsubstituted at the 16-position. Therefore, Ram et al. art fails to teach the concept of using bulk hindrance at the 16-position to protect against anti-angiogenic deactivation of the claimed estradiol derivatives.

Furthermore, the properties of the steroidal molecules at issue here are unpredictable based upon structural similarity. For example, 2-methoxy estradiol is anti-angiogenic and is useful for treating diseases such as cancer; whereas, 4-methoxy estradiol is a known carcinogen and would not be useful for treating cancer or any other disease in a human. Thus, the mere shift of the methoxy group from the 2-position to the 4-position significantly changes the properties of the estradiol derivative, and, therefore, illustrates the unpredictability of the properties of this molecule based upon structural similarity.

The MPEP states that, "The presumption of obviousness based on a reference disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (appellant produced sufficient evidence to establish a substantial degree of unpredictability in the pertinent art area, and thereby rebutted the presumption that structurally similar compounds have similar properties)." MPEP §2144.09. Applicants submit that the foregoing showing of unpredictability overcomes any alleged *prima facie* obviousness of the presently claimed compounds.

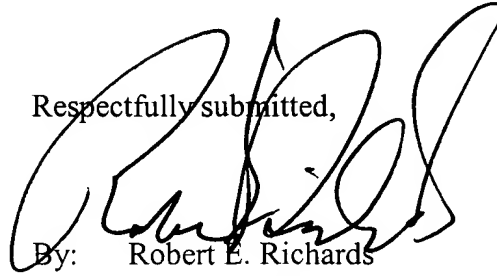
Considering the prior art and the claimed invention as a whole dictates a finding of nonobviousness of the presently claimed invention. Therefore, Claims 1-9 are not obvious under 35 U.S.C. § 103 in view of Ram et al. Accordingly, the rejection of Claims 1-9 as being obvious in view of Ram et al. should be withdrawn.

Conclusion

In view of the foregoing remarks, applicants respectfully maintain that Claims 1-9 are in condition for allowance. Such action is respectfully requested. If there are informalities remaining in the application which may be corrected by Examiner's Amendment, or there are any

other issues which can be resolved by telephone interview, a telephone call to the undersigned attorney at 404-745-2408 is respectfully solicited.

Respectfully submitted,

A large, stylized handwritten signature in black ink, appearing to read 'R. Richards', is written over the 'Respectfully submitted,' text.

By: Robert E. Richards
Reg. No. 29,105

KILPATRICK STOCKTON LLP
1100 Peachtree Street, NE, Suite 2800
Atlanta, GA 30309-4530
Telephone 404.815.6500
Docket No. 05213-0731 (43170-253406)